

## REMARKS

### *Status of the Claims*

Claims 1-2, 6-11, 16-38 are pending. Claims 1-2 and 20-22 have been amended. Claims 32-38 have been added. Claims 4 and 12-15 have been canceled without prejudice or disclaimer to the subject matter therein. Support for the amended and new claims can be found throughout the specification and in the claims as originally filed, for example, at paragraphs [012], [017], [021], [039], [046] and [048]. Applicants respectfully submit that the amended and new claims do not constitute new matter.

### *Statement of Substance of Interview Under 37 C.F.R. § 1.133(b)*

In accordance with 37 C.F.R. § 1.133(b) and M.P.E.P. § 713.04, Applicants provide a summary of the interview held on April 1, 2008 with Examiner Sajjadi. Applicants thank Examiner Sajjadi for agreeing to conduct the interview and appreciate the courtesies extended by the Examiner.

During the interview, Applicants' representatives discussed each of the rejections set forth in the Office Action. With respect to the rejection under 35 U.S.C. § 101, Applicants' representatives proposed amending claim 1 to recite "recombinant." With respect to the rejection under 35 U.S.C. § 102(b), Applicants' representatives pointed out that Soonpaa et al. does not teach the active step of "introducing" as recited in claim 1. With respect to the rejection under 35 U.S.C. § 112, 1<sup>st</sup> paragraph, Applicants' representatives explained the specification provides the requisite guidance to teach one of skill in the art how to make and use the claimed invention. Applicants' representatives also referred to the previously-filed Declaration Under 37 C.F.R. § 1.132.

### *Claim Rejections - 35 U.S.C. § 101*

Claims 1, 4, 18, 21, 23 and 24 stand rejected under 35 U.S.C. § 101 as allegedly being directed to non-statutory subject matter.

Applicants have amended claim 1 to recite "recombinant" as suggested in the Office Action. Office Action, ¶ 3. In view of the foregoing, Applicants respectfully request withdrawal of this rejection.

***Claim Rejections - 35 U.S.C. § 102(b)***

Claims 1, 4, 18, 21, 23 and 24 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Soonpaa et al. (J. Clin. Invest., 1997: 99(11): 2644-2654, hereinafter "Soonpaa").

Applicants respectfully traverse this rejection and submit that Soonpaa does not teach a method of proliferating cardiomyocytes comprising the active step of "introducing " as recited in claim 1. Indeed, nowhere does Soonpaa teach a method of "*introducing a recombinant D-type cyclin and a recombinant cyclin dependent kinase into the nucleus of cardiomyocytes.*" (emphasis added). Rather, Soonpaa only suggests that "[c]yclin D1 overexpression resulted in concomitant increase in CDK4 levels in adult myocardium." See Abstract. Accordingly, because Soonpaa does not teach each and every limitation, Applicants respectfully request that this rejection be withdrawn.<sup>1</sup>

***Claim Rejections - 35 U.S.C. § 112, First Paragraph***

Claims 1-2, 4, 6 and 16-31 stand rejected under 35 U.S.C. § 112, 1<sup>st</sup> paragraph, because the specification, while being enabling for a method of proliferating cardiomyocytes *in vitro* by introducing adenoviral vectors expressing a D-type cyclin, CDK4 or CDK6 and a nuclear localization signal, allegedly does not reasonably provide enablement for an *in vivo* method of proliferating any cardiomyocyte by introducing any D-type cyclin and either CDK4 or CDK6 into the cardiomyocyte.

Applicants respectfully traverse this rejection.

As an initial matter, Applicants point out the following evidence of record supports the *in vivo* proliferation of cardiomyocytes. First, the specification provides a working example of proliferating cardiomyocytes *in vivo*. See Example 5. Second, as discussed in a prior response, the conclusions reached in Example 5 have been acknowledged in the art. See Amendment and Response Under 37 C.F.R. § 1.116, filed March 6, 2007, pages 6-7. Third, the Declaration of Dr. Koshimizu demonstrates that CDK4 and D1NLS gene expression *in vivo* causes cell division of adult cardiomyocytes and had protective effects on cardiac dysfunction and heart failure. See Declaration of Dr. Koshimizu Under 37 C.F.R. § 1.132, ¶¶ 20-26.

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<sup>1</sup> Applicants also note that Soonpaa's discussion of cardiomyocytes (page 2651, right column, lines 10-17) is not consistent with the enhanced proliferation of cardiomyocytes. Indeed, the same result may be obtained when the cell death of cardiomyocytes are inhibited. Furthermore, the enhanced DNA synthesis and increase of multinucleated cells disclosed in Soonpaa is not direct evidence of the enhanced proliferation of cardiomyocytes.

In view of this evidence, Applicants respectfully submit that the enablement rejection should be withdrawn. Nonetheless, Applicants provide the following comments.

The Office Action cites Patel et al. for the proposition that adenoviral methodology of gene transfer in animals is complex and does necessarily equate with “success” in humans. Office Action, ¶¶ 9 and 14.

Applicants respectfully submit, however, Patel states that its own data “demonstrate the safety of direct myocardial administration of [an adenovirus vector] and *support the potential use of this strategy to treat human myocardial ischemia.*” (emphasis added). See Patel et al., Abstract. Applicants also point out that the claims are directed to methods of proliferating cardiomyocytes, not methods of treating humans *per se*. Nevertheless, Applicants note that the USPTO has granted numerous patents directed to methods of treating cardiac disease comprising administering a viral vector (or other delivery system) comprising a nucleic acid into a human. See, e.g., U.S. Patent No. 6,306,830 (directed to a method of enhancing cardiac function of a mammal with congestive heart failure); U.S. Patent No. 6,436,908<sup>2</sup> (directed to a method of inhibiting the activity of a beta adrenergic receptor kinase 1 (BARK1) so as to improve myocardial function in a mammal); U.S. Patent No. 6,589,523 (directed to a method for treating a patient suffering from dilated cardiomyopathy). Furthermore, Applicants maintain that the use of vectors (e.g., viral vectors) and other delivery systems such as liposomes may be used in connection with claimed invention. Indeed, such vectors and delivery systems are simply tools for introducing and expressing the target genes.

The Office Action cites a 2002 publication of Tamamori-Adachi et al. and a 2000 publication of Nochol et al. to support its assertion that the art is unpredictable. See Office Action, ¶¶ 10-13 and 15. The Office Action cites Tamamori-Adachi et al. for the proposition that expression of cyclin D1 and CDK4 causes cardiac hypertrophy. *Id.* at ¶ 10. The Office Action cites Nicol for the proposition that hypertrophic cardiomyopathies result in heart failure. *Id.* at ¶¶ 10-13 and 15. The Office Action also suggests that long term proliferation problems may result. *Id.* at ¶ 18.

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<sup>2</sup> These claims are not limited to viral vectors. See, e.g., claims 1 and 6.

Applicants respectfully submit that the problem of cardiac hypertrophy has been overcome by the claimed invention.<sup>3</sup> Indeed, the claimed invention results in the proliferation of cardiomyocytes and does not cause hypertrophic cardiomyopathies. This proliferation is not permanent. Rather, proliferation is induced temporarily and when cell cycle inhibitors/suppressors are expressed, proliferation is inhibited. Applicants note that the viral vectors (e.g., adenoviral vector) exemplified in the specification do not cause permanent gene expression and therefore would not lead to hyperproliferation.<sup>4</sup>

The Office Action asserts that the Declaration of Dr. Koshimizu is insufficient to overcome the enablement rejection. Office Action, ¶ 28.

As an initial matter, Applicants point out that the Office Action has not provided any evidence (e.g., peer-reviewed publications) that rebuts any of the conclusions reached by Dr. Koshimizu. Rather, as discussed in a prior response, a third party has acknowledged that the work done by the inventors shows the *in vivo* proliferation of cardiomyocytes. See Amendment and Response Under 37 C.F.R. § 1.116, filed March 6, 2007, pages 6-7. Furthermore, to the extent the Office Action suggests that human data is required (*see* Office Action, ¶ 28), Applicants submit that it is well-established that human testing is not required for patentability. See, e.g., *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995).

Nonetheless, Applicants respectfully submit that the Declaration of Dr. Koshimizu provides substantial evidence that the claimed invention is enabled. A detailed discussion of the Declaration of Dr. Koshimizu is provided in Applicants last response. The Declaration demonstrates, *inter alia*, that Dr. Koshimizu applied the claimed invention to an experimental animal (rat) using a typical virus vector and showed the effective results of heart treatment. To the extent the Office Action disagrees with the statements made by Dr. Koshimizu, Applicants respectfully submit that (1) the

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<sup>3</sup> The Office Action appears to assert that hypertrophic conditions are associated with increasing cell number (i.e., proliferation) and results in heart failure. Office Action, ¶ 13. Applicants respectfully disagree and submit that it is well known that cardiac hypertrophy causes a decrease of cell number and the volume of each single cell increases, which cause stress to the heart and results in heart failure.

<sup>4</sup> In the case where a retroviral vector is used, there is a possibility that long-term expression may be caused by the incorporation thereof into a chromosome. However, hyperproliferation would not be considered likely to occur.

Office Action does not provide any evidence to support its assertions; and (2) the Office Action appears to require a standard akin to that of the FDA.

For example, the Office Action disagrees with Dr. Koshimizu's conclusion that the D1NLS + CDK4 treatment protected ischemic hearts from left ventricular dysfunction. Office Action, ¶ 34. In particular, the Office Action states that the "D1NLS group still has significant cardiac dysfunction compared to the Sham group." *Id.*

The Office Action fails to cite any evidence in support of these assertions. Furthermore, Applicants respectfully submit that it is a general interpretation of one of skill in the art that the recovery of the heart function to the same level of the sham group is almost impossible in such a heart failure model of experimental animal. Accordingly, Applicants maintain that the data of Table 1 demonstrates the effectiveness of D1NLS group.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, 1<sup>st</sup> paragraph.

### CONCLUSION

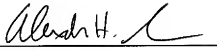
It is believed that these amendments and remarks should place this application in condition for allowance. A notice to that effect is respectfully solicited. If the Examiner has any questions relating to this response or the application in general he is respectfully requested to contact the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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